ORIGINAL ARTICLE

Malignant pleural effusion as a predictor of the efficacy of anti-PD-1 antibody in patients with non-small cell lung cancer

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Abstract

Background: The aim of this study was to evaluate the usefulness of the presence of malignant pleural effusion (MPE) as a negative predictor of anti-PD-1 antibody efficacy.

Methods: A retrospective review of patients with advanced or recurrent non-small cell lung cancer treated with an anti-PD-1 antibody between December 2015 and March 2018 at the National Cancer Center Hospital, Japan, was conducted. Progression-free survival (PFS) and overall survival (OS) were compared between patients with and without MPE. Additional survival analysis according to PD-L1 expression status was conducted. Univariate and multivariate analyses were performed.

Results: A total of 252 patients were identified before the commencement of anti-PD-1 antibody treatment: 33 with MPE and 219 without MPE. PFS and OS were significantly shorter in patients with MPE than in patients without MPE (median PFS 3.0 vs. 5.8 months, hazard ratio [HR] 1.7, $P = 0.014$; median OS 7.9 vs. 15.8 months, HR 2.1, $P = 0.001$). In patients with PD-L1 expression in $\geq$ 1% of their tumor cells, the PFS of patients with MPE was significantly shorter than of patients without MPE (median PFS 3.1 vs. 6.5 months, HR 2.0, 95% confidence interval 1.0–3.5; $P = 0.021$). The presence of MPE was independently associated with a shorter PFS and OS in multivariate analysis.

Conclusion: The presence of MPE in patients administered an anti-PD-1 antibody is associated with shorter PFS and OS, regardless of the presence of PD-L1 expression $\geq$ 1% of tumor cells.

Introduction

PD-1/PD-L1 checkpoint inhibitors, such as nivolumab, pembrolizumab, and atezolizumab, exhibit definite antitumor activity for the treatment of advanced non-small cell lung cancer (NSCLC) and enable longer progression-free survival (PFS) and overall survival (OS) periods than cytotoxic drugs. These agents are now approved and have become standard treatment options for patients with NSCLC. PD-L1 expression in tumor cells is a predictor of the efficacy of PD-1/PD-L1 checkpoint inhibitors and is used for making treatment strategy decisions. In patients with advanced NSCLC and positive PD-L1 expression in $\geq$

50% of their tumor cells, pembrolizumab has become the standard of care for first-line treatment.[1] However, the response rate remains approximately 45%, and approximately 30% of patients progress during the first three months of pembrolizumab treatment. PD-L1 expression alone is not sufficient as a definitive predictor, thus there remains a need to identify other predictors or patient characteristics capable of predicting the response of patients to PD-1/PD-L1 checkpoint inhibitors.

Malignant pleural effusion (MPE) occurs in approximately 15% of lung cancer patients.[2] MPE is managed using several treatment options, including pleural drainage,

pleurodesis, and pleuroperitoneal shunts. The presence of MPE is known to be an independent predictor of poor survival in patients with advanced NSCLC.[3] For most patients with a good performance status whose lungs re-expand after pleural drainage, systemic chemotherapy is recommended, as it is for patients without MPE. Some chemotherapeutic regimens containing an anti-vascular endothelial growth factor (VEGF) antibody, such as bevacizumab, have shown promising efficacy and a high MPE control rate.[4–7] This tendency has also been observed with molecular target drugs, which have a higher efficacy than cytotoxic agents. Recent studies examining *EGFR*-mutated NSCLC patients administered EGFR-tyrosine kinase inhibitors (TKIs) have shown that the presence of MPE at baseline is associated with shorter PFS and OS.[8,9] These findings suggest that the presence of MPE might be a strong negative predictor of the efficacy of some agents.

Several studies have shown that the efficacy of PD-1/PD-L1 checkpoint inhibitors is correlated with several patient characteristics. *EGFR* mutation, a never-smoker status, and a poor performance status (PS) were all correlated with a lower efficacy of PD-1/PD-L1 checkpoint inhibitors, compared to *EGFR* wild-type, smoker status, and a good PS, respectively.[10–15] A previous study also reported that the presence of liver or lung metastases was a negative predictor of anti-PD-1 efficacy in patients with advanced NSCLC. However, no previous reports have compared the efficacy of anti-PD-1 antibodies between NSCLC patients with and without MPE. Thus, we retrospectively investigated the efficacy of anti-PD-1 antibodies in advanced NSCLC patients with or without MPE.

Methods

Patients

We retrospectively reviewed the medical records of patients with advanced or recurrent NSCLC who received nivolumab or pembrolizumab as first, second, or third-line treatment between 1 December 2015 and 31 March 2018 at the National Cancer Center Hospital, Japan. The end of the follow-up period was 31 July 2018.

Patients with positive pleural fluid cytology results, pleural effusion requiring drainage, or presenting with multiple pleural nodules and nodular pleural thickening with pleural effusion on a computed tomography (CT) scan were diagnosed as having MPE. We diagnosed the presence of MPE before commencing anti-PD-1 antibody treatment.

Tumor response was assessed according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 using CT images. We did not consider an increase in pleural effusion as a progressive event.

PFS was defined as the interval between the first dose of anti-PD-1 antibody treatment and the date of clinical or radiographic disease progression or death from any cause; in the absence of confirmation of disease progression or death, data were censored at the last date the patient was known to be alive. OS was defined as the interval between the first dose of anti-PD-1 antibody treatment and the date of death from any cause; in the absence of confirmation of death, data were censored at the last date the patient was known to be alive.

PD-L1 expression in the tumor cells of patients with NSCLC was analyzed using the commercially available PD-L1 immunohistochemistry 22C3 pharmDx assay (Dako; Agilent Technologies, Santa Clara, CA, USA).[16] Positive PD-L1 expression in ≥ 1% of all tumor cells was classified as a positive result, while positive PD-L1 expression in ≥ 50% was classified as strongly positive, consistent with the methodology used in other studies involving anti-PD-1 antibodies (Fig 1).[1,17,18]

Statistical analysis

Baseline characteristics were compared between patients with and without MPE using the Fisher's exact test for categorical variables. PFS and OS curves were estimated using the
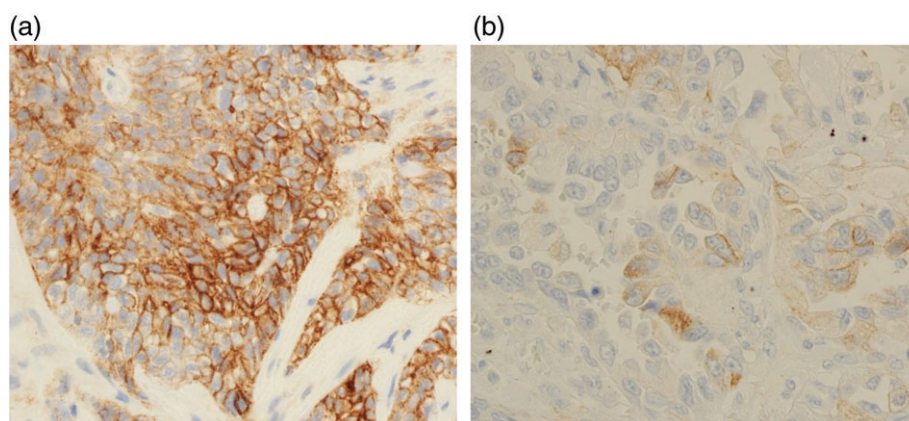

(a)　　　　　　　　　　(b)

Figure 1 Immunohistochemical analysis of PD-L1 expression in (**a**) strongly positive (≥ 50%) and (**b**) positive (≥ 1%) tumor cells.

Kaplan–Meier method, and differences according to the absence or presence of MPE were evaluated using a log-rank test. Univariate and multivariate analyses were performed using Cox proportional hazard regression models for performance status, smoking status, *EGFR* mutational status, PD-L1 expression status, treatment line, and the presence of MPE. The covariates other than MPE were adopted based on the results of recent trials suggesting that they might affect the efficacy of PD-1/PD-L1 checkpoint inhibitors.[1,11,13–15,17,19,20] All *P* values were based on a one-sided hypothesis, and values < 0.05 were considered statistically significant. All statistical analyses were performed using JMP Pro version 13.0.0 (SAS Institute, Cary, NC, USA).

Results

Patient characteristics

A total of 252 patients with advanced or recurrent NSCLC administered nivolumab or pembrolizumab were identified.

The patient characteristics are summarized in Table 1. Twelve percent of the patients had an Eastern Cooperative Oncology Group PS of ≥ 2, 19% were never-smokers, 7.9% had *EGFR* mutations, 13% had a PD-L1 negative status, and 84% received an anti-PD-1 antibody as second or third-line treatment. Of the 252 patients, 33 patients had MPE (cytologically confirmed malignant cells, *n* = 20; pleural effusion drainage, *n* = 26; presence of pleural lesions, *n* = 6). The baseline characteristics were not significantly different between patients with and without MPE. The median follow-up period was 7.4 (range: 0.4–27.5) months.

Efficacy

The overall response rate (ORR) was similar in patients with and without MPE (ORR 24% vs. 26%; *P* = 0.49) (Table 2). Although there was no statistical significance, the disease control rate (DCR) in the patients with MPE was lower than in patients without MPE (DCR 58%

Table 1 Baseline characteristics (*n* = 252)

| Characteristics | All, N (%) | Malignant pleural effusion | | *P* |
		No, N (%)	Yes, N (%)	
Patients	252	219	33	
Age				
Median (range)	61 (30–83)	63 (33–83)	61 (30–79)	
≥ 75 years	28 (11)	25 (11)	3 (9.1)	0.48
Gender				0.49
Male	172 (68)	150 (68)	22 (66)	
ECOG PS				0.094
0–1	221 (88)	195 (89)	26 (79)	
≥ 2	31 (12)	24 (11)	7 (21)	
Smoking status				0.14
Never-smoker	47 (19)	38 (17)	9 (27)	
Current or former smoker	200 (79)	176 (80)	24 (73)	
Histology				0.078
Adenocarcinoma	162 (64)	135 (62)	27 (82)	
Squamous	58 (23)	54 (25)	4 (12)	
Other	32 (13)	30 (14)	2 (6)	
Clinical stage				0.35
III/IV	186 (74)	163 (74)	23 (70)	
Recurrence	66 (26)	56 (26)	10 (30)	
EGFR mutated	20 (7.9)	17 (7.8)	3 (9.1)	0.61
PD-L1 22C3 status				0.33
< 1%	33 (13)	27 (12)	6 (18)	
≥ 1%	132 (52)	114 (52)	18 (55)	
Brain metastasis	55 (22)	50 (23)	5 (15)	0.23
Treatment line				0.062
1	41 (16)	32 (15)	9 (27)	
2/3	211 (84)	187 (85)	24 (73)	
Anti-PD-1 antibody				0.34
Nivolumab	179 (71)	157 (72)	22 (67)	
Pembrolizumab	73 (29)	62 (28)	11 (33)	

ECOG PS, Eastern Cooperative Oncology Group performance status.

Table 2 Response to anti-PD-1 antibody

Response	Malignant pleural effusion		
	No (*n* = 219)	Yes (*n* = 33)	*P*
Best overall response, N (%)			
Complete response	1 (0.5)	0 (0)	
Partial response	57 (26)	8 (24)	
Stable disease	69 (32)	6 (18)	
Progressive disease	84 (38)	17 (52)	
Not evaluable	8 (3.7)	2 (6)	
Objective response, N (%, 95% CI)	58 (26, 21–33)	8 (24, 13–41)	0.49
Disease control, N (%, 95% CI)	127 (58, 51–64)	14 (42, 27–59)	0.068

CI, confidence interval.

vs. 42%; *P* = 0.068). None of the patients with MPE showed an increase in MPE before a progressive event. The subsequent treatment rate after disease progression among patients administered an anti-PD-1 antibody was similar between patients with and without MPE (57% vs. 56%; *P* = 1.00). The PFS and OS of patients with MPE were significantly shorter than in patients without MPE (median PFS 3.0 vs. 5.8 months, hazard ratio [HR] 1.7, 95% confidence interval [CI] 1.1–2.5, *P* = 0.014; median OS 7.9 vs. 15.8 months, HR 2.1; 95% CI 1.3–3.3, *P* = 0.001) (Fig 2).

Additional survival analysis of all patients grouped according to PD-L1 expression was performed. In the group with strongly positive PD-L1 expression, the PFS of the patients with MPE was shorter but not significantly different from that of patients without MPE (median PFS 5.9 vs. 8.1 months, HR 1.8, 95% CI 0.75–3.9; *P* = 0.14)

(Fig 3a). In the PD-L1 expression-positive group, the PFS of patients without MPE was significantly shorter than of patients with MPE (median PFS 3.1 vs. 6.5 months, HR 2.0. 95% CI 1.0–3.5; *P* = 0.021) (Fig 3b).

Multivariate analysis showed that the presence of MPE was significantly and independently associated with shorter PFS (HR 2.0, 95% CI 1.1–3.5; *P* = 0.019) and OS (HR 2.4, 95% CI 1.2–4.6; *P* = 0.011) (Table 3). As is well known, first-line treatment was significantly associated with longer PFS (HR 0.55, 95% CI 0.28–0.99; *P* = 0.046). In addition, a good PS was independently associated with longer OS (HR 0.38, 95% CI 0.19–0.83; *P* = 0.018).

Discussion

In this retrospective study we showed that in patients who received anti-PD-1 antibodies, those with MPE had significantly shorter PFS and OS than those without MPE, and the presence of MPE was an independent negative predictor affecting PFS and OS, regardless of the presence of positive PD-L1 expression.
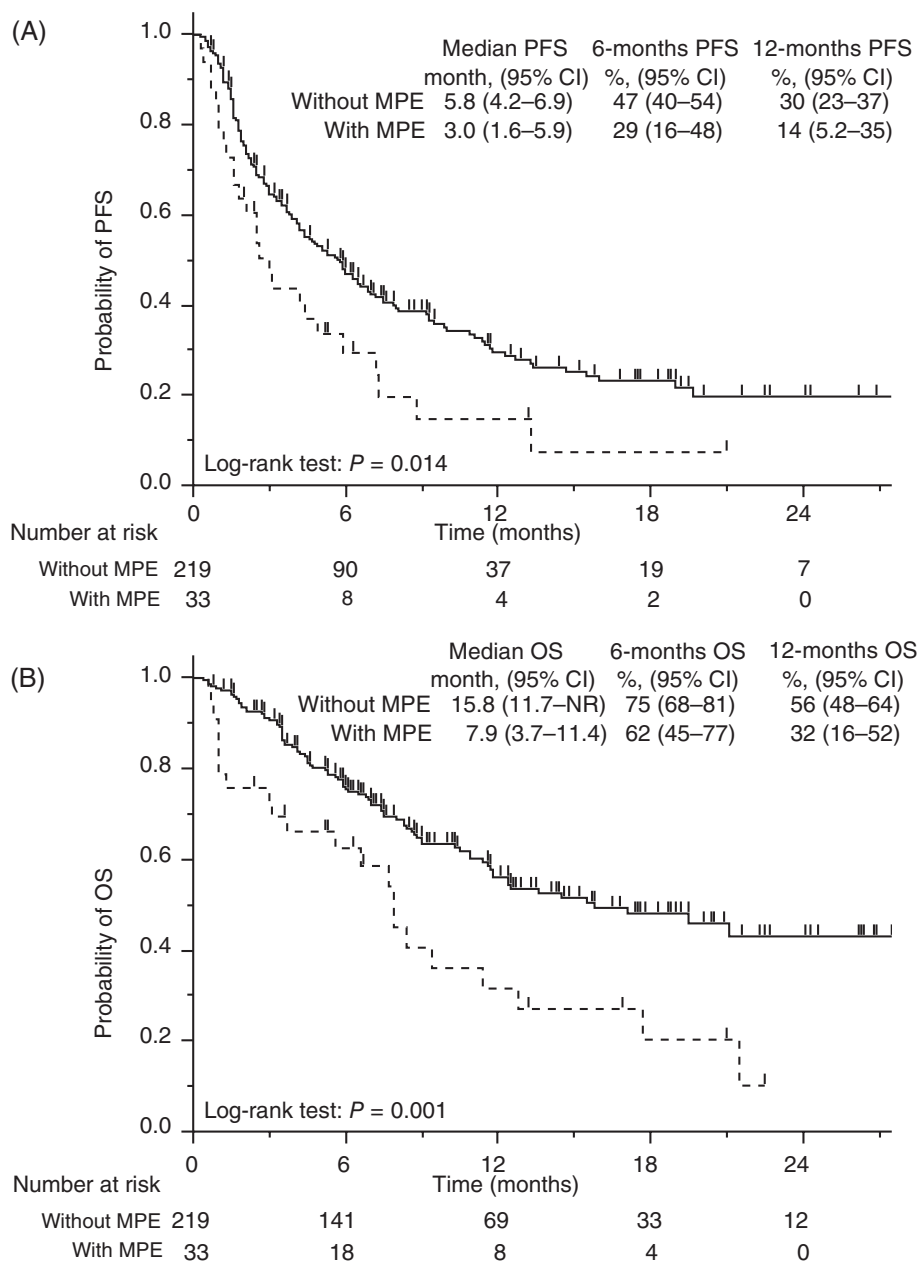
Pleural effusion is often found during the clinical course of advanced lung cancer. MPE results from increased fluid production as a result of increased capillary permeability secondary to tumor implantation on the pleural surface or impaired fluid resorption caused by tumor invasion into the pleuromediastinal lymphatic system. The presence of MPE is reportedly an independent predictor of poor survival in patients with advanced NSCLC.[2,3] Several studies have shown that VEGF plays a pivotal role in the pathogenesis of MPE and that the level of VEGF in plasma is relatively high in patients with MPE.[21–23] VEGF promotes the development of MPE by increasing vascular

Table 3 Cox proportional hazard regression analyses

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P*	HR (95% CI)	*P*
PFS				
Malignant pleural effusion (+/−)	1.7 (1.1–2.5)	0.023	2.0 (1.1–3.5)	0.019
ECOG PS (2–3/0–1)	2.1 (1.3–3.1)	0.003	1.5 (0.74–2.7)	0.24
Smoking status (never/current or former)	1.9 (1.3–2.7)	0.002	1.5 (0.80–2.7)	0.2
EGFR mutated (+/−)	1.8 (1.0–2.9)	0.043	0.80 (0.29–1.9)	0.63
PD-L1 status (≥ 1%/< 1%)	0.59 (0.38–0.94)	0.026	0.61 (0.36–1.1)	0.085
Treatment line (1/2–3)	0.61 (0.37–0.96)	0.03	0.55 (0.28–0.99)	0.046
OS				
Malignant pleural effusion (+/−)	2.1 (1.3–3.3)	0.003	2.4 (1.2–4.6)	0.011
ECOG PS (2–3/0–1)	3.1 (2.1–5.4)	<0.001	2.7 (1.2–5.3)	0.018
Smoking status (never/current or former)	1.1 (0.70–1.8)	0.61	0.95 (0.45–1.8)	0.87
EGFR mutated (+/−)	1.1 (0.49–2.0)	0.88	0.15 (0.008–0.73)	0.013
PD-L1 status (≥1%/<1%)	0.53 (0.32–0.90)	0.021	0.55 (0.29–1.1)	0.075
Treatment line (1/2–3)	0.95 (0.52–1.6)	0.85	0.86 (0.38–1.8)	0.7

CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; OS, overall survival; PFS, progression free survival.

Figure 2 Kaplan–Meier curves of (**a**) progression-free survival (PFS) and (**b**) overall survival (OS) of all patients. CI, confidence interval; MPE, malignant pleural effusion; NR, not reached. (——) Without MPE, and (·······) With MPE.

(A)

	Median PFS month, (95% CI)	6-months PFS %, (95% CI)	12-months PFS %, (95% CI)
Without MPE	5.8 (4.2–6.9)	47 (40–54)	30 (23–37)
With MPE	3.0 (1.6–5.9)	29 (16–48)	14 (5.2–35)

Log-rank test: *P* = 0.014

Number at risk

	0	6	12	18	24
Without MPE	219	90	37	19	7
With MPE	33	8	4	2	0

(B)

	Median OS month, (95% CI)	6-months OS %, (95% CI)	12-months OS %, (95% CI)
Without MPE	15.8 (11.7–NR)	75 (68–81)	56 (48–64)
With MPE	7.9 (3.7–11.4)	62 (45–77)	32 (16–52)

Log-rank test: *P* = 0.001

Number at risk

	0	6	12	18	24
Without MPE	219	141	69	33	12
With MPE	33	18	8	4	0

permeability and by promoting angiogenesis.[24] VEGF is also known as an important regulatory factor that activates host vascular endothelial cells and promotes malignant proliferation, increasing oxygen and nutrients for tumor metastasis.[25] On the other hand, VEGF has recently been identified as a key factor in tumor-induced immunosuppression. In a mouse model, infusion of VEGF promoted the production of granulocyte-differentiation antigen-1-positive myeloid-derived suppressor cells (MDSCs) and blocked dendritic cell development.[26] MDSCs cause the development of other immunosuppressive cells, such as

regulatory T cells.[27,28] VEGF also decreased the cytotoxic activity of T cells expressing VEGF receptor 2, which was recovered by an anti-VEGF antibody.[29] Our results may be biologically plausible because VEGF may lead to the development of MPE and the ineffectiveness of the anti-PD-1 antibody.

Several trials have shown that PD-L1 expression is a predictor of the efficacy of PD-1/PD-L1 checkpoint inhibitors. Pembrolizumab is highly effective in NSCLC patients with positive PD-L1 expression in ≥ 50% of their tumor cells.[1] PD-L1 expression is also associated with the
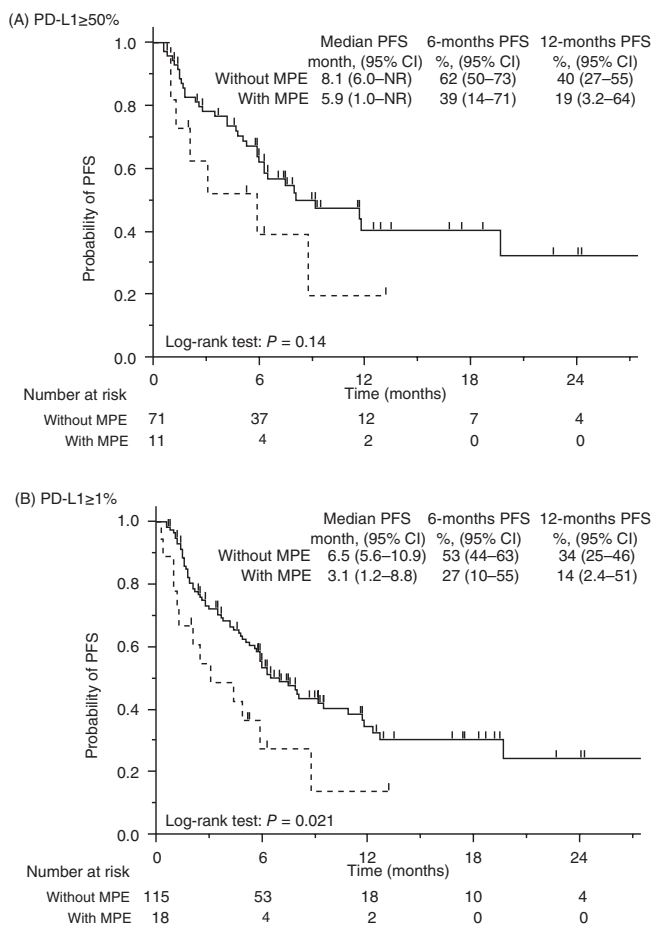
(A) PD-L1≥50%

	Median PFS month, (95% CI)	6-months PFS %, (95% CI)	12-months PFS %, (95% CI)
Without MPE	8.1 (6.0–NR)	62 (50–73)	40 (27–55)
With MPE	5.9 (1.0–NR)	39 (14–71)	19 (3.2–64)

Log-rank test: P = 0.14

Number at risk

Without MPE	71	37	12	7	4
With MPE	11	4	2	0	0

(B) PD-L1≥1%

	Median PFS month, (95% CI)	6-months PFS %, (95% CI)	12-months PFS %, (95% CI)
Without MPE	6.5 (5.6–10.9)	53 (44–63)	34 (25–46)
With MPE	3.1 (1.2–8.8)	27 (10–55)	14 (2.4–51)

Log-rank test: P = 0.021

Number at risk

Without MPE	115	53	18	10	4
With MPE	18	4	2	0	0

Figure 3 Kaplan–Meier curves of progression-free survival (PFS) in patients with PD-L1 expression in (**a**) ≥ 50% of tumor cells and (**b**) ≥ 1% of tumor cells. MPE, malignant pleural effusion; NR, not reached. (———) Without MPE, and (··········) With MPE.

efficacy of other PD-1/PD-L1 checkpoint inhibitors[13,20] However, even if PD-L1 expression is strongly positive, some patients exhibit disease progression immediately after receiving PD-1/PD-L1 checkpoint inhibitors. Therefore, additional predictors and patient characteristics are needed for optimal patient selection to achieve a good outcome and to avoid initial tolerance. Several subgroup analyses and retrospective studies have revealed that a poor PS, never-smoker status, and *EGFR* mutations are negative predictors of the efficacy of PD-1/PD-L1 checkpoint inhibitors. Our results suggest that the presence of MPE could also be a strong negative predictor. Despite having a high PD-L1 expression level, patients with MPE tended to have shorter PFS than those without MPE. Moreover, in multivariate analysis, the presence of MPE showed stronger associations with poor PFS than a poor PS, never smoking, *EGFR* mutations, or negative PD-L1 expression.

In contrast, Tamiya *et al.* previously reported that liver or lung metastases, but not MPE, were predictors of efficacy in NSCLC patients administered anti-PD-1 antibodies.[19] Moreover, the proportion of patients diagnosed with MPE in their sample was higher than in ours (44% vs. 13%). Some studies have reported that the incidence of MPE in lung cancer patients is approximately 15%,[2,30,31] which is similar to our result. The discrepancy in results between the study by Tamiya *et al.* and ours, in which patients with MPE had shorter PFS than those without MPE, is most likely the result of differences in the definition of MPE. Cancer-related pleural effusion can be classified as MPE or paramalignant pleural effusion. Paramalignant pleural effusion is associated with bronchial obstruction and distal pneumonitis, prior mediastinal irradiation, and hypoalbuminemia.[32] These facts may suggest that Tamiya *et al.* included patients with paramalignant pleural effusions who would not have been diagnosed as such in our study.

Our study had several limitations. First, this study was conducted based on a retrospective review of medical records. Most of the patients had cytologically confirmed MPE, but pleural fluid cytology results were not available for some of the patients in the sample. Therefore, we classified patients with pleural effusion requiring drainage or those who presented with pleural nodules and nodular pleural thickening as having MPE, regardless of the cytology results. Second, consensus criteria for assessing the response of patients with MPE have not yet been established. We used RECIST version 1.1 and did not count an increase in pleural effusion as a progression event. Therefore, the reported PFS of patients with MPE in this trial might have been longer than the actual PFS. Finally, we did not examine the correlation between VEGF level and the efficacy of PD-1/PD-L1 checkpoint inhibitors. A recent study has shown that patients receiving a drug combination that included bevacizumab had fewer MDSCs, and larger numbers of type 1 helper T cells and cytotoxic T lymphocytes after treatment compared to patients who did not receive the drug combination.[33] These efficacies are thought be a result of the reduction in MDSCs arising from treatment with bevacizumab, possibly leading to the recovery of effective antitumor immunity. Clinical trials of drug combinations including a PD-1/PD-L1 checkpoint inhibitor and agents targeting VEGF/VEGFR are underway for several kinds of cancer, including NSCLC. These future studies may help to clarify the mechanisms behind this phenomenon.

In conclusion, this study showed that the presence of MPE is a negative predictor of anti-PD-1 antibody efficacy in patients with advanced NSCLC. Therefore, future studies evaluating new treatment strategies for MPE in patients receiving anti-PD-1 antibody are required.

Disclosure

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